IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the patent application of: Carter and Gennings

Serial No. 10/655,540 Group Art Unit 1631

Filed 09/05/2003 Examiner: Russell Negin

For: ***"EXPERIMENTAL DESIGN AND DATA ANALYTICAL METHODS FOR DETECTING AND CHARACTERIZING INTERACTION THRESHOLDS ON FIXED RATIO RAYS OF POLYCHEMICAL MIXTURES AND SUBSETS THEREOF"***

Commissioner of Patents and Trademarks
Washington, D.C. 20231

DECLARATION OF RICHARD ALLAN CARCHMAN, Ph.D.
UNDER 37 C.F.R. § 1.132

Sir:

1. I hold the degree of Ph.D. in pharmacology from SUNY Downstate Medical Center, and have previously been employed as a Professor of the Department of Pharmacology/Toxicology and as an Affiliate Professor of the Department of Biostatistics at Virginia Commonwealth University (Richmond, VA). I subsequently worked for Philip Morris USA (Richmond VA) and am a retired Vice President of that organization.

I have attached a copy of my *curriculum vitae*. Some of the highlights which demonstrate my expertise include the following: I have had over three decades of experience in research both in academia and in industry; I have over eighty published articles in refereed journals; I am a Journal reviewer for a number of highly respected journals; I have trained a large number of graduate students and post doctoral researchers both in industry and academia; I have been on fifty Ph.D. faculty advisory committees; I have edited a volume of the Journal of the American College of Toxicology; and I have been the principal investigator on a large number of research projects. I am qualified as an expert in the fields of pharmacology and toxicology, and I am competent to provide testimony on the level of skill of one of ordinary skill in the art in these

fields particularly as they relate to the subject matter in USSN 10/655,540, and the state of the art including testimony on the presence of a long felt need in the art to which USSN 10/655,540 pertains.

2. I am currently a Principal of Solveritas, a biotechnology company located in the Biotechnology Center of the Medical College of Virginia/Virginia Commonwealth University. Solveritas is the licensee of the technology disclosed in US patent application 10/655,540.

3. In my opinion, one of ordinary skill in the art would hold a degree of MD or a PhD in pharmacology, toxicology, biology, biochemistry, biostatistics or a related subject. He or she would be aware of the possible hazards of drug or agent interactions and problems and challenges associated with methods for assessing potential interactions. One of ordinary skill in the art would know that the patent application describes the use of statistical methods to assess or predict drug/agent interactions, and he or she would be well versed in statistics as statistical methods are used widely in the fields of pharmacology and toxicology.

4. In my opinion, the assessment of drug and/or agent interactions has become more and more important with time, as increasing numbers of drugs are prescribed to individual patients and multiple chemical agents are released into the environment. It is well documented that the exposure of an individual to multiple agents may result in effects that contradict an assumption of additivity. In other words, one or more of the agents may influence the effect of one or more of the other agents in the group, and the effect may be to increase the activity of an agent (synergy) or to decrease the effect of an agent (antagonism). Both of these effects can have profound consequences to individuals who are exposed to the drug/agent mixture.

Tests of drug or agent interactions are typically carried out in a suitable animal model. When only a small number of agents is considered, the logistics of testing a sufficient number of animals at a sufficient number of doses to obtain statistically meaningful data about possible interactions may be manageable. However, as the number of agents in a group increases, the number of data points necessary to draw meaningful conclusions from the data (factorial data) increases sharply, making thorough testing impractical or impossible. Thus, in my opinion, there has been a long felt need in the art for analytical methods that can be used to assess potential interactions among large numbers of agents in the absence of exhaustive test data, i.e. using relatively few data points with or without data obtained with single agents (single chemical data).

Copies of two authoritative articles confirming this long felt need are attached and summarized as follows:

Teuschler et al., (2002) states that "The SOT [Society of Toxicology] Expert Working Group concluded that the scientific challenges of chemical mixture toxicology and risk assessment are substantial and warrant considerable attention" and further discusses the "need to move mixture research beyond current scientific methods and practices" (first paragraph of second column, page 35). In particular, the paper recommends that "New methods can include: (1) computational technology; (2) mathematical/statistical modeling..." and observes that "Given that exhaustively testing all mixtures of concern in the laboratory is impractical, predictive tools are needed to focus on specific exposures." (Column 2, page 37). The authors also state that "Progress is most likely, therefor, when the focus is on cooperative interactions between toxicologists interested in experimental studies of mechanisms, *statisticians with expertise in experimental design...*" (Emphasis added; last sentence of page 37). One of skill in the art, upon reading this paper, would conclude that, at the time of publication of the paper, the long felt need for practical methods to predict drug/agent interactions, in the absence of obtaining exhaustive, factorial data, had not been met.

Monosson (2005) states that "the U.S. EPA Risk Assessment Guidance for Superfund acknowledges that 'simultaneous subthreshold exposure to several chemicals could result in an adverse health effect' such that estimates based on single chemicals might underestimate the overallrisk (U.S. EPA 1989)". However, "in the absence of evidence of chemical interaction, assumption of no interaction is the default approach" for risk assessment of chemical mixtures. Two component-based approaches are used as default assumptions. "Dose addition is suggested for chemicals that have similar toxicologic end points". "The dose addition methodology assumes that the potency of each chemical in the mixture can be calculated relative to each other or to one common chemical". In contrast, response addition is the recommended default assumption "for chemicals that act so differently – the presence of one chemical in no way affects the toxicity of another chemical [U.S, EPA 2000]." Thus, one of skill in the art, upon reading this paper, would conclude that, at the time of publication of the paper, the long felt need for practical methods to predict drug/agent interactions was not met and was largely based on default assumptions of no interaction – even given the understanding that subthreshold exposures

could result in adverse health effects.

5. I have read and understand the Office Action mailed on May 30, 2007 and the references cited therein (Gennings et al., 1997 and Gennings et al., 1998). In my opinion, one of ordinary skill in the art would recognize that neither of these two references alone or in combination provides or suggests a sufficient solution to the problem of analyzing and predicting the interactions of chemicals (drugs/agents) in the absence of factorial data.

Upon reading Gennings 1997, one of ordinary skill in the art would understand how to use single chemical data to develop a flexible threshold model under the assumption of additivity using single chemical data, and to detect departures from additivity using the model. Upon reading Gennings 1998, one of skill in the art would understand how to use a threshold model supported by full fixed ratio rays to detect and characterize departures from additivity at specified mixtures of interest. Upon reading one or both of these references, one of ordinary skill in the art would not understand how to extend such analyses by using both full and reduced rays, i.e. by eliminating agents from the mixture, testing the remaining subset of agents, and analyzing the data to detect and characterize departures from additivity within the subset, or to use the results of such an analysis to identify which agents interact with each other, in the absence of factorial data. However, upon reading the present patent application, one of skill in the art would know how to carry out such an analysis by using both full and reduced rays, and would realize that the results of such analyses can be used, for example, to identify which agents in a mixture are influencing the activity of other agents, even in the absence of exhaustive, factorial data. One of ordinary skill in the art would recognize and appreciate that such an analysis would make optional or eliminate the need for obtaining extensive experimental results.

In summary, one of ordinary skill in the art would conclude that, even several years after the Gennings 1997 and Gennings 1998 articles were published, the long felt need for methods to analyze data and predict chemical interactions in the absence of factorial data, had not been met. In particular, the solution presented in the subject patent application did not occur to those of ordinary skill in the art even after the publication of the two Gennings articles. Therefore, the two Gennings articles did not, either alone or in combination, provide or suggest a solution to those of ordinary skill in the art.

6. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above-referenced application and any patent issuing thereon.

Date _____ Signed _____

Richard A. Carchman